PCT/DK 2004/000574

Kongeriget Danmark

Patent application No.: PA 2003 01232

Date of filing: 29 August 2003

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Title: Pharmaceutical compositions comprising tacrolimus and/or an analogue thereof

IPC: -

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21 September 2004

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PATENT- OG VAREMÆRKESTYRELSEN

Pharmaceutical compositions comprising tacrolimus and/or an analogue thereof

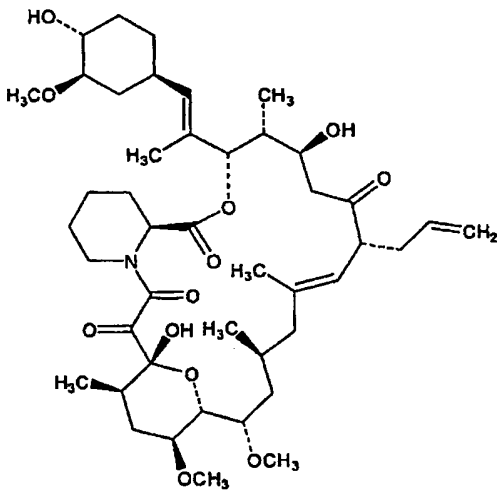
Field of the Invention

The present invention relates to pharmaceutical compositions in particulate form or in solid dosage forms comprising tacrolimus and/or an analogue thereof. Compositions of the invention exhibit markedly increased bioavailability of tacrolimus and/or an analogue thereof compared to commercially available solid dosage forms containing tacrolimus. Furthermore, compositions according to the invention provide for a significant reduced food effect and a delayed release of tacrolimus is expected to reduce the number of gastro-intestinal related side effects.

In particular the invention relates to solid pharmaceutical compositions comprising tacrolimus and/or an analogue thereof dissolved in a solid carrier formulated for oral administration.

Background of the invention

Tacrolimus or FK-506 or FR-900506 has the tricyclic structure shown below.



$C_{44}H_{69}NO_{12}$

Tacrolimus appears in the form of white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol and very soluble in methanol and chloroform.

Within the scope of the present invention is tacrolimus in any physical form (crystals, amorphous powder, any possible polymorphs, any possible solvates include the hydrate, anhydrate, complexes thereof etc.). Included is also any analogue of tacrolimus, pharmaceutically acceptable salts, solvates, complexes and prodrugs thereof.

The preparation of tacrolimus is described in EP-A-0 184 162 and/or analogues thereof are disclosed e.g. in EP-A-0 444 659 and US 6,387,918 which is hereby incorporated by reference.

Tacrolimus is a macrolide compound with useful immunosuppressive activity, antimicrobial activity and other pharmacological activities and is of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft versus host diseases, autoimmune diseases and infectious diseases.

Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow and small bowel and pancreas, lung and trachea, skin, cornea and limb.

In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis and graft-versus-host disease.

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggest that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells, a nuclear component thought to initiate gene transcription for the formation of lymphokines. The net result is the inhibition of T-lymphocyte activation, i.e. immunosupression.

A commercially available tacrolimus-containing product is Prograf®. Prograf® is indicated for the prophylaxis of organ rejection in patients recieiving allogeneic liver or kidney transplants.

Usually tacrolimus is administered orally and is therefore absorbed from the gastrointestinal tract. It has been observed that the absorption is negatively influenced by

the simultaneous ingestion of food. Thus, the rate and extent of tacrolimus absorption were greatest under fasted conditions.

In general, it is known that the absorption and bioavailability of a therapeutically active substance can be affected by a variety of factors when administered orally. Such factors include the presence of food in the gastrointestinal tract and, in general, the gastric residence time of a drug substance is significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug substance is affected beyond a certain point due to the presence of food in the gastrointestinal tract, the drug substance is said to exhibit a food effect. Food effects are important because there is a risk associated with administering the drug substance to a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remedy the condition for which the drug was administered.

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The bioavailability is generally as low as at the most about 20% after oral administration. Plasma peak concentrations are usually reached within 1-3 hours after oral administration.

Furthermore, oral administration of tacrolimus is associated with side effects including high levels of gastrointestinal side effects. Frequently observed side effects are tremor, headache, hypertension, renal dysfunction, hyperkalemia, hypomagnesemia, hyperglycemia, insomnia, diarrhea, nausea, constipation and abdominal pain.

For oral administration, tacrolimus is currently formulated and marketed as soft gelatine capsules comprising the equivalent of 0.5, 1 or 5 mg anhydrous tacrolimus and marketed under the trade name Prograf ® and Protropic®.

There remains a need for new pharmaceutical compositions comprising tacrolimus exhibiting, increased bioavailability of the active compound and/or reduced or eliminated food effect. In particular it is desired to obtain quicker and larger uptake of the active compound, and thereby provide for a reduction of the administered dosages. Since tacrolimus has been shown to exhibit a number of adverse side effects the latter is a particular important object. Further, pharmaceutical compositions comprising tacrolimus and exhibiting a higher bioavailability of this compound may allow a reduction in the dosage units taken by a patient, e.g. down to a single dose daily, and may also reduce or

negate the need for food to be takes simultaneously with the dosage form thereby allowing patients more freedom on when the drug is taken.

Delaying the release of tacrolimus to the distal part of duodenum is expected to reduce the drug related gastro-intestinal related side effects and owing to the compositions/technology, this is done without loosing systemic bioavailability.

Description of the invention

As mentioned above, there is a need for developing pharmaceutical tacrolimus-containing compositions notably for oral use that lead to an improved treatment of conditions with tacrolimus. An improved bioavailability will lead to an improved treatment because it will be possible to obtain the same therapeutic response with a decreased tacrolimus dose and this in turn will lead to a significant reduction in dose-related side-effects. Another way of obtaining an improved treatment of conditions where tacrolimus is indicated is by balancing the release of tacrolimus and/or an analogue thereof to the gastro-intestinal tract in such a manner that an enhanced plasma concentration of tacrolimus and/or an analogue thereof is obtained initially or delayed with respect to the time of administration. A further therapeutic improvement would be to develop modified or delayed release compositions containing tacrolimus, but in practice this is mostly of interest if it is possible overall to improve the bioavailability.

The present invention provides pharmaceutical compositions and solid dosage forms for improved treatment of conditions that respond to tacrolimus treatment.

Delayed release is mainly brought about by some kind of enteric coating. Whereas semipermeable coating will show some kind of delayed release, it does not preciously enough "delay" release. Additionally it requires a certain amount of time to release the content. The coating sought for this invention, is a pH dependant coating. This type of coating is very resistant to release of drug until a certain pH is reached. Within very few 1/10'th of pH, the film alters properties and becomes permeable. Examples of pH-sensitive polymers, which are relatively insoluble and impermeable at the pH of the stomach, but which are more soluble and permeable at the pH of the small intestine and colon include, but not limited to:

polyacrylamides, phthalate derivatives such as acid phthalates of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, methylcellulose phthalate, polyvinyl acetate

phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate, styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers, polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, shellac, and vinyl acetate and crotonic acid copolymers.

pH-sensitive polymers of specific interest include shellac; phthalate derivatives, particularly cellulose acetate phthalate, polyvinylacetate phthalate, and hydroxypropylmethylcellulose phthalate; polyacrylic acid derivatives, particularly polymethyl methacrylate blended with acrylic acid and acrylic ester copolymers; and vinyl acetate and crotonic acid copolymers.

The present invention provides pharmaceutical compositions and solid dosage forms for improved treatment of conditions that respond to tacrolimus treatment.

In one aspect, the present invention relates to a pharmaceutical composition in particulate form comprising tacrolimus and/or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof exhibits an $AUC/AUC_{Prograf®}$ value of at least about 1.3, the AUC values being determined under similar conditions.

As it appears from the Examples herein the bioavailability obtained after administration of a composition according to the invention is markedly improved. Thus, in specific embodiments, the $AUC/AUC_{Prograf®}$ value is at least about 1.5 such as about 1.75 or more, about 1.8 or more, about 1.9 or more, about 2.0 or more, about 2.5 or more, about 2.75 or more, about 3.0 or more, about 3.25 or more, about 3.5 or more, about 3.75 or more, about 4.0 or more, about 4.25 or more, about 4.5 or more, about 4.75 or more or about 5.0 or more, the AUC values being determined under similar conditions.

Thus, it has surprisingly been found that the pharmaceutical compositions according to the invention exhibit surprisingly higher bioavailability compared to commercially available formulations such as Prograf®. In fact the bioavailability of tacrolimus can according to the invention be increased by over 200 % compared with the said commercially available products.

In general, the change in bioavailability and/or the changes in other bioavailability related parameters are normally determined by *in vivo* studies in a suitable animal model testing

the compositions in question together with e.g. Prograf® or a similar commercially available tacrolimus-containing product. The use of a dog model for establishing evidence of the bioavailability of certain formulations is general practice in the pharmaceutical industry.

The studies relevant for tacrolimus are non-radomized, cross-over studies, where each dog is it's own control. Four dogs, and four treatments are normally applied. As no iv injections are given, the bioavailabilities obtained are relative.

Further it has surprisingly been found that the need for simultaneous food intake in order to secure a sufficient uptake of tacrolimus is significantly reduced or even completely abolished.

Thus, the pharmaceutical compositions according to the invention provide significant higher bioavailability of tacrolimus, which may reduced the number of daily administered dosage units, and reduce or abolish the need for administration in connection with food intake, which provide for a higher degree of freedom for the recipient of the pharmaceutical compositions, and consequently the patients acceptance and/or compliance may be significantly improved.

As mentioned above, one of the major challenges with respect to formulation of tacrolimus compositions is to avoid an adverse food effect. In general, tacrolimus is much better absorbed when it is administered orally together with food. A great variation in bioavailability is therefore seen following administration with or without food. This dependency makes it difficult to give precise guidelines as to how large a dose that should be administered and, furthermore, it requires information to the patient about the dosing regime. The present invention aims at providing compositions wherein the adverse food effect is reduced. Thus, the present invention provides a composition, which does not exhibit a significant adverse food effect after administration of the composition to a mammal in need of such a treatment as evidenced by a value of (AUC_{fed}/AUC_{fasted}) of at least about 0.85 with a lower 90% confidence limit of at least 0.75.

More specifically, a pharmaceutical composition according to the invention has a value of (AUC_{fed}/AUC_{fasted}) of about 0.9 or more such as, e.g., about 0.95 or more, about 0.97 or more or about 1 or more.

A further advantage of a composition of the present invention is the possibility of obtaining an effective therapeutic response with a decreased dosage compared to traditional oral treatment. Accordingly, upon oral administration to a mammal in need thereof a pharmaceutical composition according to the invention releases tacrolimus or an analogue thereof in a pH-dependant manner and the composition is essentially bioequivalent with Prograf® or a similar commercially available tacrolimus-containing product when administered in a dosis that is at the about most about 85% w/w such as, e.g., at the most about 80% w/w, at the most about 75%, at the most about 70% w/w, at the most about 65% w/w, at the most about 60% w/w, at the most about 55% w/w or at the most about 50% w/w of the dose of tacrolimus administered in the form of Prograf® or a similar commercially available tacrolimus-containing product.

Parameters often used in bioequivalence studies are t_{max}, c_{max}, $AUC_{0\text{-infinity}}$, $AUC_{0\text{-}t}$. Other relevant parameters may be W_{50}, W_{75} and/or MRT. Accordingly, at least one of these parameters may be applied when determining whether bioequivalence is present. Furthermore, in the present context, two compositions are regarded as bioequivalent if value of the parameter used is within 80-125% of that of Prograf® or a similar commercially available tacrolimus-containing product used in the test.

In the present context "t_{max}" denotes the time to reach the maximal plasma concentration (c_{max}) after administration; $AUC_{0\text{-infinity}}$ denotes the area under the plasma concentration versus time curve from time 0 to infinity; $AUC_{0\text{-}t}$ denotes the area under the plasma concentration versus time curve from time 0 to time t; W_{50} denotes the time where the plasma concentration is 50% or more of C_{max}; W_{75} denotes the time where the plasma concentration is 75% or more of C_{max}; and MRT denotes mean residence time for tacrolimus (and/or an analogue thereof).

Two other main disadvatages associated with treatment or prophylaxis with tacrolimus is the relative high incidence of gatrointestinal side effects and a relatively high inter-individual variation. It is envisaged that a composiiton according to the invention will lead to a reduction in unwnanted side effects, especially gastrointestinal related side effects. The reduction may be in terms of reduced frequency or in terms of severity. The side effects in question includes e.g. diarrhe, constipation, abdominal pain, nausea etc. In one aspect the invention concerns a pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and

reduces gastro-intestinal side effects compared to those of Prograf® administered under the same conditions and in a dose that provides an equivalent therapeutic effect.

Increasing the bioavailability, the Area Under the Curve, will normally reduce the intra- and inter- variability related to absorption of a drug substance. This is particularly true; whenever the low and impaired bioavailability is a consequence of poor water solubility. It is contemplated that compositions according to the invention will provide CV's on Area under Curve data that are significantly smaller than with Prograf® and like products.

Furthermore, it is envisaged that a pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient - and wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner - reduces inter- and/or intra-individual variations compared to those of Prograf® administered under the same conditions and in a dose that provides an equivalent therapeutic effect.

In a specific aspect, the invention provides a pharmaceutical composition or a solid dosage form that releases tacrolimus and/or an analogue thereof relatively fast so as to enable a relatively fast onset of therapeutic effect. Accordingly, the invention relates to a pharmaceutical composition in particulate form comprising tacrolimus and/or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof in a pH-dependant manner releases at least about 50% w/w of the total amount of tacrolimus and/or an analogue thereof within about 15 hours such as, e.g., within about 12 hours.

More specifically, upon oral administration to a mammal in need thereof a composition according to the invention releases at least about 50% w/w of the total amount of tacrolimus and/or an analogue thereof within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours or within about 3 hours.

In a further embodiment, upon oral administration to a mammal in need thereof a pharmaceutical composition according to the invention releases at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus and/or an analogue thereof within about 15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours.

Furthermore or alternatively, at least about 50% w/w of the total amount of tacrolimus and/or an analogue thereof is released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5. Guidance for a suitable dissolution test is described in the Examples herein, but variations with respect to the specific method employed and the ingredients contained in the dissolution medium etc. are within the scope of the present invention. A person skilled in the art will know how to carry out a suitable dissolution test e.g. with guidance from USP, Ph.Eur. and the like. Suitable conditions for the *in vitro* dissolution test are employing USP dissolution test (paddle method) and a buffer pH 7.5 containing 2.5% SDS and 1g/mL of pancreatin as dissolution medium.

In other embodiments, the following conditions are fulfilled with respect to *in vitro* dissolution test:

i) at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours, within about 3 hours or within about 2 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5

ii) at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 1.5 hours such as, e.g., within about 1 hour, within about 0.75 hours, within about 0.5 hours or within about 20 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

iii) at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof is released within about15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5

iv) at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof is released within about 5 hours such as, e.g., within about 4 hours, within about 3 hours, within about 2 hours, within about 1

hours or within about 30 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5, and/or

v) at least about 20% w/w such as, e.g., at least about 25% w/w, at least about 30% w/w, at least about 35% w/w or at least about 40% w/w of the total amount of tacrolimus or an analogue thereof is released within the first 3 hours such as, e.g., within the first 2 hours or within the first hour when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

In an interesting embodiment, the composition is designed to have a delayed release of tacrolimus and/or an analogue thereof. Therefore, the invention also includes a pharmaceutical composition in particulate form comprising tacrolimus and/or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof has a delayed release of tacrolimus and/or an analogue thereof so that at the most 10% w/w such as, e.g., at the most about 7.5% w/w or at the most about 5% w/w of the total amount of tacrolimus or an analogue thereof is released within the first two hours such as, e.g., within the first hour after administration.

In other embodiments, the following conditions are fulfilled with respect to *in vitro* dissolution test performed under acidic conditions:

i) at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w, at the most about 15% w/w or at the most about 10% w/w of tacrolimus or an analogue thereof is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5,

ii) at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 5% w/w or at the most about 2.5% w/w of tacrolimus or an analogue thereof is released within 2 hours in an In vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5

iii) at the most about 60% w/w such as, e.g., at the most about 50% w/w, at the most about 40% w/w or at the most about 30% w/w of tacrolimus or an analogue thereof is

released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5

iv) at the most about 40% w/w such as, e.g., at the most about 30% w/w, at the most about 25% w/w or at the most about 20% w/w of tacrolimus or an analogue thereof is released within 6 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5, and/or

v) at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w or at the most about 15% w/w of tacrolimus or an analogue thereof is released within 4 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

The pharmaceutical compositions may be prepared by any convenient method such as, e.g. granulation, mixing, spray drying etc. A particularly useful method is the method described in WO 03/004001. Herein is described a process for the preparation of particulate material by a controlled agglomeration method, i.e. a method, which enables a controlled growth in particle size. The method involves spraying a first composition comprising e.g. tacrolimus and a carrier, which has been melted, onto a second solid carrier medium. Normally, the meltable carrier has a melting point of at least 5 °C but lower than the melting point of tacrolimus. The melting point of the carrier may be in the range of 10 °C to 150 °C, such as, e.g., in the range of 30 °C to 100°C or in the range of 40 °C to 50 °C is most preferred.

It is within the skills of the average practioner to select a suitable carrier being pharmaceutical acceptable, capable of dispersing or at least partly dissolving tacrolimus and having a melting point in the desired range using general knowledge and routine experimentation. Suitable candidate for carriers are described in WO 03/004001, which is herein incorporated by reference.

In the present context, suitable carriers are e.g. those mentioned as an oil or an oily-like material (as discussed later herein) as well as those disclosed in WO 03/004001.

An advantage of using the controlled agglomeration method described in WO 03/004001 is that it is possible to apply a relatively large amount of a melt to a particulate material without having an undesirable growth in particle size. Accordingly, in one embodiment of the invention, the particulate material of a pharmaceutical composition has a geometric weight mean diameter d_{gw} of ≥10 μm such as, e.g. ≥20 μm, from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500 μm, from about 100 to about 1000 μm or from about 100 to about 700 μm, or at the most about 400 μm or at the most 300 μm such as, e.g., from about 50 to about 400 μm such as, e.g., from about 50 to about 350 μm, from about 50 to about 300 μm, from about 50 to about 250 μm or from about 100 to about 300 μm.

Pharmaceutically acceptable excipients

In the present context the terms "pharmaceutically acceptable excipient" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, cosmetic and/or foodstuff composition, which have acceptable technical properties.

Examples on suitable excipients for use in a composition or solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the composition or solid dosage form according to the invention may be used for different purposes, the choice of excipients is normally made taken such different uses into considerations. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents, chelating agents, coloring agents, complexing agents, emulsifying and/or solubilizing agents, flavors and perfumes, humectants, sweetening agents, wetting agents etc.

Examples on suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C,

Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the second composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in a composition or solid dosage form of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

Other additives in a composition or a solid dosage form according to the invention may be antioxidants like e.g. ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium

metabisulfite, propyl gallate, sodium formaldehylde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherol acetate, tocopherol hemisuccinate, TPGS or other tocopherol derivatives, etc. The carrier composition may also contain e.g. stabilising agents. The concentration of an antioxidant and/or a stabilizing agent in the carrier composition is normally from about 0.1 % w/w to about 5% w/w.

A composition or solid dosage form according to the invention may also include one or more surfactants or substances having surface-active properties. It is contemplated that such substances are involved in the wetting of the slightly soluble active substance and thus, contributes to improved solubility characteristics of the active substance.

Examples on surfactants are given in the following.

Suitable excipients for use in a composition or a solid dosage form according to the invention are surfactants such as, e.g., hydrophobic and/or hydrophilic surfactants as those disclosed in WO 00/50007 in the name of Lipocine, Inc. Examples on suitable surfactants are

i) polyethoxylated fatty acids such as, e.g. fatty acid mono- or diesters of polyethylene glycol or mixtures thereof such as, e.g. mono – or diesters of polyethylene glycol with lauric acid, oleic acid, stearic acid, myristic acid, ricinoleic acid, and the polyethylene glycol may be selected from PEG 4, PEG 5, PEG 6, PEG 7, PEG 8, PEG 9, PEG 10, PEG 12, PEG 15, PEG 20, PEG 25, PEG 30, PEG 32, PEG 40, PEG 45, PEG 50, PEG 55, PEG 100, PEG 200, PEG 400, PEG 600, PEG 800, PEG 1000, PEG 2000, PEG 3000, PEG 4000, PEG 5000, PEG 6000, PEG 7000, PEG 8000, PEG 9000, PEG 1000, PEG 10,000, PEG 15,000, PEG 20,000, PEG 35,000,

ii) polyethylene glycol glycerol fatty acid esters, i.e. esters like the above-mentioned but in the form of glyceryl esters of the individual fatty acids;

iii) glycerol, propylene glycol, ethylene glycol, PEG or sorbitol esters with e.g. vegetable oils like e.g. hydrogenated castor oil, almond oil, palm kernel oil, castor oil, apricot kernel oil, olive oil, peanut oil, hydrogenated palm kernel oil and the like,

iv) polyglycerized fatty acids like e.g. polyglycerol stearate, polyglycerol oleate, polyglycerol ricinoleate, polyglycerol linoleate,

v) propylene glycol fatty acid esters such as, e.g. propylene glycol monolaurate, propylene glycol ricinoleate and the like,

vi) mono- and diglycerides like e.g. glyceryl monooleate, glyceryl dioleae, glyceryl mono- and/or dioleate, glyceryl caprylate, glyceryl caprate etc.;

vii) sterol and sterol derivatives;

viii) polyethylene glycol sorbitan fatty acid esters (PEG-sorbitan fatty acid esters) such as esters of PEG with the various molecular weights indicated above, and the various Tween ® series;

ix) polyethylene glycol alkyl ethers such as, e.g. PEG oleyl ether and PEG lauryl ether;

x) sugar esters like e.g. sucrose monopalmitate and sucrose monolaurate;

xi) polyethylene glycol alkyl phenols like e.g. the Triton® X or N series;

xii) polyoxyethylene-polyoxypropylene block copolymers such as, e.g., the Pluronic® series, the Synperonic® series, Emkalyx®, Lutrol®, Supronic® etc. The generic term for these polymers is "poloxamers" and relevant examples in the present context are Poloxamer 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403 and 407;

xiii) sorbitan fatty acid esters like the Span® series or Ariacel® series such as, e.g. sorbinan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate etc.;

xiv) lower alcohol fatty acid esters like e.g. oleate, isopropyl myristate, isopropyl palmitate etc.;

xv) ionic surfactants including cationic, anionic and zwitterionic surfactants such as, e.g. fatty acid salts, bile salts, phospholipids, phosphoric acid esters, carboxylates, sulfates and sulfonates etc.

When a surfactant or a mixture of surfactants is present in a composition or a solid dosage form of the invention, the concentration of the surfactant(s) is normally in a range of from about 0,1 – 80% w/w such as, e.g., from about 0.1 to about 20% w/w, from about 0.1 to about 15% w/w, from about 0.5 to about 10% w/w, or alternatively, from about 0.10 to about 80% w/w such as, e.g. from about 10 to about 70% w/w, from about 20 to about 60% w/w or from about 30 to about 50% w/w.

In a specific aspect of the invention, the at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

Such materials are is especially useful as a sorption material for oils or oily-like materials in pharmaceuticals, cosmetics and/or foodstuff. In a specific embodiment, the material is used as a sorption material for oils or oily-like materials in pharmaceuticals. The material that has the ability to function as a sorption material for oils or oily-like materials is also denoted "oil sorption material". Furthermore, in the present context the term "sorption" is used to denote "absorption" as well as "adsorption". It should be understood that whenever one of the terms is used it is intended to cover the phenomenon absorption as well as adsorption.

Notably, the pharmaceutically acceptable excipient may comprise a silica acid or a derivative or salt thereof such as, e.g., silicon dioxide or a polymer thereof as a pharmaceutically acceptable excipient. Dependent on the quality employed a silicon dioxide may be a lubricant or it may be an oil sorption material. Qualities fulfilling the latter function seem to be most important.

In a specific embodiment, a composition or solid dosage form according to invention comprises a pharmaceutically acceptable excipient that is a silicon dioxide product that has properties corresponding to Zeofree® 5161A, Zeofree® 5162, Zeofree® 5175A, Zeopharm® 80 (available from J. M. Huber, Hamina, Finland), Aeroperl® 300, Sident® 22S, Sipernat®160, Sipernat® 160PQ, Sipernat® 22, Sipernat® 22 LS, Sipernat® 22, Sipernat® 22 LS, Sipernat® 22S, Sipernat® 2200, Sipernat® 310, Sipernat® 320, Sipernat® 320 DS, Sipernat® 325 C, Sipernat® 35, Sipernat® 350, Sipernat® 360, Sipernat® 383 D8, Sipernat® 44, Sipernat® 44MS, Sipernat® 50, Sipernat® 50S, Sipernat® 50 S, Sipernat® 500 LS, or Sipernat® 570 (available from Degussa, Frankfurt, Germany).

As it appears from the examples herein, a very suitable material is Aeroperl® 300 (including materials with properties like or corresponding to those of Aeroperl® 300).

Use of an oil sorption material in compositions or dosage forms according to the invention is very advantageous for the preparation of pharmaceutical, cosmetic, nutritional and/or food compositions, wherein the composition comprises oil or an oily-like material. One of the advantages is that is it possible to incorporate a relatively large amount of oil and oily-like material and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of oil or oily-like materials by use of an oil sorption material according to the invention. Within the pharmaceutical field it is an advantage to

be able to incorporate a relatively large amount of an oil or an oily-like material in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, delayed, sustained and/or pulsed delivery of the active substance. Thus, in a specific embodiment it is used in the preparation of pharmaceutical compositions.

The oil sorption material for use in the processing into solid compositions normally absorbs about 5% w/w or more, such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily material and is still a solid material.

An important aspect of the invention is compositions or solid dosage forms comprising an oil or an oily-like material.

Oil or oily-like materials

In the present context the term "Oils and oily-like materials" is used in a very broad sense including oils, waxes, semi-solid materials and materials that normally are used as solvents (such as organic solvents) or cosolvents within the pharmaceutical industry, and the term also includes therapeutically and/or prophylactically active substances that are in liquid form at ambient temperature; furthermore the term includes emulsions like e.g. microemulsions and nanoemulsions and suspensions. The oils and oily-like materials that can be absorbed will normally be liquid at ambient or elevated temperature (for practical reasons the max. temperature is about 250 °C). They may be hydrophilic, lipophilic, hydrophobic and/or amphiphilic materials.

The oils and oily-like material that are suitable for use in the present context are substances or materials, which have a melting point of at least about 0 °C and at the most about 250 °C.

In specific embodiments of the invention, the oil or oily-like material has a melting point of about 5 °C or more such as, e.g., about 10 °C or more, about 15 °C or more, about 20 °C or more or about 25 °C or more.

In further embodiments of the invention, the oil or oily-like material has a melting point of at least about 25 °C such as, e.g., at least about 30 °C at least about 35 °C or at least about 40 °C. For practical reasons, the melting point may normally not be too high, thus, the oil or oily-like material normally has a melting point of at the most about 300 °C such as, e.g., at the most about 250 °C, at the most about 200 °C, at the most about 150 °C or at the most about 100 °C. If the melting point is higher a relatively high temperature may promote e.g. oxidation or other kind of degradation of an active substance in those cases where e.g. a therapeutically and/or prophylactically active substance is included.

In the present context, the melting point is determined by DSC (Differential Scanning Calorimetry). The melting point is determined as the temperature at which the linear increase of the DSC curve intersects the temperature axis (see Fig. 1 for further details).

Interesting oils or oily-like materials are generally substances, which are used in the manufacture of pharmaceuticals as so-called melt binders or solid solvents (in the form of solid dosage form), or as co-solvents or ingredients in pharmaceuticals for topical use.

It may be hydrophilic, hydrophobic and/or have surface-active properties. In general hydrophilic and/or hydrophobic oils or oily-like materials are suitable for use in the manufacture of a pharmaceutical composition comprising a therapeutically and/or prophylactically active substance that has a relatively low aqueous solubility and/or when the release of the active substance from the pharmaceutical composition is designed to be immediate or non-modified. Hydrophobic oil or oily-like materials, on the other hand, are normally used in the manufacture of a modified release pharmaceutical composition. The above-given considerations are simplified to illustrate general principles, but there are many cases where other combinations of oils or oily-like materials and other purposes are relevant and, therefore, the examples above should not in any way limit the invention.

Typically, a suitable hydrophilic oil or oily-like material is selected from the group consisting of: polyether glycols such as, e.g., polyethylene glycols, polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers and mixtures thereof, or it may be selected from the group consisting of: xylitol, sorbitol, potassium sodium tartrate, sucrose tribehenate, glucose, rhamnose, lactitol, behenic acid, hydroquinon monomethyl ether,

sodium acetate, ethyl fumarate, myristic acid, citric acid, Gelucire 50/13, other Gelucire types such as, e.g., Gelucire 44/14 etc., Gelucire 50/10, Gelucire 62/05, Sucro-ester 7, Sucro-ester 11, Sucro-ester 15, maltose, mannitol and mixtures thereof.

A suitable hydrophobic oil or oily-like material may be selected from the group consisting of: straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as e.g., cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as, e.g. stearic acid, myristic acid, palmitic acid, higher alcohols such as, e.g., cetanol, stearyl alcohol, low melting point waxes such as, e.g., glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, or a mixture thereof.

In an interesting embodiment, the oil or oily-like material is a polyethylene glycol having an average molecular weight in a range of from about 400 to about 35,000 such as, e.g., from about 800 to about 35,000, from about 1,000 to about 35,000 such as, e.g., polyethylene glycol 1,000, polyethylene glycol 2,000, polyethylene glycol 3,000, polyethylene glycol 4,000, polyethylene glycol 5,000, polyethylene glycol 6000, polyethylene glycol 7,000, polyethylene glycol 8,000, polyethylene glycol 9,000 polyethylene glycol 10,000, polyethylene glycol 15,000, polyethylene glycol 20,000, or polyethylene glycol 35,000. In certain situations polyethylene glycol may be employed with a molecular weight from about 35,000 to about 100,000.

In another interesting embodiment, the oil or oily-like material is polyethylene oxide having a molecular weight of from about 2,000 to about 7,000,000 such as, e.g. from about 2,000 to about 100,000, from about 5,000 to about 75,000, from about 10,000 to about 60,000, from about 15,000 to about 50,000, from about 20,000 to about 40,000, from about 100,000 to about 7,000,000 such as, e.g., from about 100,000 to about 1,000,000, from about 100,000 to about 600,000, from about 100,000 to about 400,000 or from about 100,000 to about 300,000.

In another embodiment, the oil or oily-like material is a poloxamer such as, e.g. Poloxamer 188, Poloxamer 237, Poloxamer 338 or Poloxamer 407 or other block copolymers of ethylene oxide and propylene oxide such as the Pluronic® and/or Tetronic® series. Suitable block copolymers of the Pluronic® series include polymers having a molecular

weight of about 3,000 or more such as, e.g. from about 4,000 to about 20,000 and/or a viscosity (Brookfield) from about 200 to about 4,000 cps such as, e.g., from about 250 to about 3,000 cps. Suitable examples include Pluronic® F38, P65, P68LF, P75, F77, P84, P85, F87, F88, F98, P103, P104, P105, F108, P123, F123, F127, 10R8, 17R8, 25R5, 25R8 etc. Suitable block copolymers of the Tetronic® series include polymers having a molecular weight of about 8,000 or more such as, e.g., from about 9,000 to about 35,000 and/or a viscosity (Brookfield) of from about 500 to about 45,000 cps such as, e.g., from about 600 to about 40,000. The viscosities given above are determined at 60 °C for substances that are pastes at room temperature and at 77 °C for substances that are solids at room temperature.

The oil or oily-like material may also be a sorbitan ester such as, e.g., sorbitan di-isostearate, sorbitan dioleate, sorbitan monolaurate, sorbitan monoisostearate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesqui-isostearate, sorbitan sesquioleate, sorbitan sesquistearate, sorbitan tri-isostearate, sorbitan trioleate, sorbitan tristearate or mixtures thereof.

The oil or oily-like material may of course comprise a mixture of different oils or oily-like materials such as, e.g., a mixture of hydrophilic and/or hydrophobic materials.

Other suitable oils or oily-like materials may be solvents or semi-solid excipients like, e.g. propylene glycol, polyglycolised glycerides including Gelucire 44/14, complex fatty materials of plant origin including theobroma oil, carnauba wax, vegetable oils like e.g. almond oil, coconut oil, corn oil, cottonseed oil, sesame oil, soya oil, olive oil, castor oil, palm kernels oil, peanut oil, rape oil, grape seed oil etc., hydrogenated vegetable oils such as, e.g. hydrogenated peanut oil, hydrogenated palm kernels oil, hydrogenated cottonseed oil, hydrogenated soya oil, hydrogenated castor oil, hydrogenated coconut oil; natural fatty materials of animal origin including beeswax, lanolin, fatty alcohols including cetyl, stearyl, lauric, myristic, palmitic, stearic fatty alcohols; esters including glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; liquid interesterified semi-synthetic glycerides including Miglycol 810/812; amide or fatty acid alcolamides including stearamide ethanol, diethanolamide of fatty coconut acids, acetic acid esters of mono and di-glycerides, citric acid esters of mono and di-glycerides, lactic acid esters of mono and diglycerides, mono and di-glycerides, poly-glycerol esters of fatty acids, poly-glycerol poly-ricinoleate, propylene glycol esters of fatty acids, sorbitan monostearates, sorbitan tristearates, sodium stearoyl lactylates, calcium stearoyl lactylates, diacetyl tartaric acid esters of mono and di-glycerides etc.

Normally, a pharmaceutical composition or a solid dosage form according to the invention has a concentration of the oil or oily-like material in the composition of about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more.

In specific embodiments the concentration of the oil or oily-like material in a composition or solid dosage form of the invention is in a range from about 20% to about 80% w/w such as, e.g., from about 25% to about 75% w/w.

One of the advantages is that is it possible to incorporate a relatively large amount of oil and olly-like material and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of oil or oily-like materials by use of an oil sorption material according to the invention. Within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of an oil or an oily-like material in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, delayed, sustained and/or pulsed delivery of the active substance.

A further advantage is that the particulate material obtained is a free-flowing powder and therefore readily processable into e.g. solid dosage forms such as tablets, capsules or sachets. Normally, the particulate material has properties that are suitable in order to manufacture tablets by direct compression without addition of large amounts of further additives. A suitable test for test the flowability of the particulate material is the method described in Ph.Eur. and measuring the flow rate of the material out of a funnel with a nozzle (orifice) diameter of 10.0 mm.

In an important embodiment of the invention, at least a part of tacrolimus and/or an analogue thereof is present in the composition in the form of a solid dispersion including a molecular dispersion and a solid solution. Normally, 10% or more such as, e.g., 20% or

more, 30% or more, 40% or more, 50% or more, 60% or more, 70% or more, 80% or more, 90% or more such as, e.g., 95% or more or about 100% w/w of tacrolimus and/or an analogue thereof is present in the composition in the form of a solid dispersion.

A solid dispersion may be obtained in different ways e.g. by employing organic solvents or by dispersing or dissolving the active substance in another suitable medium (e.g. an oil or an oily-like material that is in liquid form at room temperature or at elevated temperatures).

Description of a solid dispersion based on organic solvents

Solid dispersions (solvent method) are prepared by dissolving a physical mixture of the active substance (e.g. a drug substance) and the carrier in a common organic solvent, followed by evaporation of the solvent. The carrier is often a hydrophilic polymer. Suitable organic solvents include pharmaceutical acceptable solvent in which the active substance is soluble such as methanol, ethanol, methylene chloride, chloroform, ethylacetate, acetone or mixtures thereof.

Suitable water soluble carriers include polymers such as polyethylene glycol, poloxamers, polyoxyethylene stearates, poly -ε-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA (Kollidon VA64), poly-methacrylic polymers (Eudragit RS, Eudragit RL, Eudragit NE, Eudragit E) and polyvinyl alcohol (PVA), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, and poly(ethylene oxide) (PEO).

Polymers containing acidic functional groups may be suitable for solid dispersions, which release the active substance in a preferred pH range providing acceptable absorption in the intestines. Such polymers may be one ore more selected from the group comprising hydroxypropyl methylcellulose phtalate (HMPCP), polyvinyl acetate phtalate (PVAP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), alginate, carbomer, carboxymethylcellulose, methacrylic acid copolymer (Eudragit L, Eudragit S), shellac, cellulose acetate phthalate (CAP), starch glycolate, polacrylin, methyl cellulose acetate phtalate, hydroxypropyulcellulose acetate phthalate, cellulose acetate terephtahalate, cellulose acetate isophthalate and cellulose acetate trimellitate.

In relations to amounts of the active substance and the polymer in the solid dispersion, the weight ratio of active substance to polymer may be in a range of from about 3:1 to about 1:20. However, narrower ranger of from about 3:1 to about 1:5, such as, e.g., from about 1:1 to about 1:3 or about may also be used.

The solid dispersion is preferably formed by spray drying techniques, controlled agglomeration, freeze-drying or coating on carrier particles or any other solvent removal process. The dried product contains the active substance present in the form of a solid dispersion including a molecular dispersion and a solid solution.

As an alternative to the use of organic solvents the drug and polymer may be co-grinded or extruded at elevated temperatures (melt extrusion).

The pharmaceutical compositions comprising tacrolimus at least partly in form of a solid dispersion or solution may in principle be prepared using any suitable procedure for preparing pharmaceutical compositions known within the art.

Apart from using the organic solvent based method, solid dispersion or solid solutions of tacrolimus and/or an analogue thereof may be obtained by dispersing and/or dissolving tacrolimus in the carrier composition used in the controlled agglomeration method. Stabilizing agents etc. may be added in order to ensure the stability of the solid dispersion/solution.

In another aspect, the invention relates to a method for the preparation of a pharmaceutical composition according to the invention. In general, any suitable method within the pharmaceutical field may be employed. However, in order to enable incorporation of a relatively high amount of an oil or an oily-like material especially the method described in WO 03/004001 (by the same inventors) has proved satisfactory. Details concerning the method are given in the above-identified publication, which is hereby incorporated by reference as well as in the Examples herein. In short, the invention provide a process for preparing a particulate pharmaceutical material comprising tacrolimus and/or an analogue thereof which method comprises spraying a first composition in liquid form, said composition comprising a carrier and having a melting point greater than 5°C onto a second composition comprising a support, said second composition being in the fluidised state and having a temperature less than the melting point of the carrier. In principle the active substance may be present in the carrier composition and/or in the second composition. However, in those cases where tacrolimus and/or an analogue thereof should be present in the composition at least partly as a solid dispersion, it is advantageous to incorporate or dissolve tacrolimus and/or an analogue thereof in the carrier composition.

Solid dosage forms

A pharmaceutical composition according to the invention is in particulate form and may be employed as such. However, in many cases it is more convenient to present the composition in the form of granules, pellets, microspheres, nanoparticles and the like or in the form of solid dosage forms including tablets, capsules and sachets and the like. A solid dosage form according to the invention may be a single unit dosage form or it may in the form of a polydepot dosage form contain a multiplicity of individual units such as, e.g., pellets, beads and/or granules.

Normally, a pharmaceutical composition or a solid dosage form of the invention is intended for administration via the oral, buccal or sublingual administration route.

The invention also relates to the above-mentioned presentation form. Within the scope of the invention are compositions/solid dosage forms that are intended to release tacrolimus and/or an analogue thereof in a fast release, a delayed release or modified release manner.

A solid dosage form according to the present invention comprises a pharmaceutical composition in particulate form as described above. The details and particulars disclosed under this main aspect of the invention apply *mutatis mutandis* to the other aspects of the invention. Accordingly, the properties with respect to increase in bioavailability, changes in bioavailability parameters, reduction in adverse food effect as well as release of tacrolimus and/or an analogue thereof etc. described and/or claimed herein for pharmaceutical compositions in particulate form are analogues for a solid dosage form according to the present invention.

Normally, the concentration of the pharmaceutical composition in particulate form is in a range of from about 5 to 100% w/w such as, e.g., from about 10% to about 90% w/w, from about 15% to about 85% w/w, from about 20% to about 80% w/w, from about 25% to about 80% w/w, from about 30% to about 80% w/w, from about 35% to about 80% w/w, from about 40% to about 75% w/w, from about 45% to about 75% w/w or from about 50% to about 70% w/w of the dosage form. In an embodiment of the invention, the concentration of the pharmaceutical composition in particulate form is 50% w/w or more of the dosage form.

A solid dosage form according to the invention is obtained by processing the particulate material according to the invention by means of techniques well-known to a person skilled

in the art. Normally, it involves further addition of one or more of the pharmaceutically acceptable excipients mentioned herein.

The composition or solid dosage form according to the invention may be designed to release tacrolimus and/or an analogue thereof in any suitable manner provided that the increase in bioavailability is present. Thus, the active substance may be released relatively fast in order to obtain an enhanced on-set of action, it may be released so as to follow zero or first order kinetics or it may be released in a controlled or modified manner in order to obtain a predetermined pattern of release. Plain formulations are also within the scope of the present invention.

The recommended dosage range for Prograf® is 0.1 to 0.2 mg/kg/day given every 12 hours in two divided doses. More importantly the blood levels has to be monitored. The typical level for 1 – 3 months is 7 –20 ng/mL and 4 – 12 months the levels should be 5 – 15 ng/mL. This is only guiding values and may vary from types of transplant and "race".

The following is for Kidney transplant patients.

	Caucasian n = 114		Black n = 56	
Time After Transplant	Dose (mg/kg)	Trough Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (ng/mL)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5
Month 12	0.13	10.1	0.19	11.0

The expected dosage recommendation for products of the present invention will be from 0.02 mg/kg/day to 0.15 mg/kg/day, dosed once a day.

The composition or solid dosage form according to the invention may also be coated with a film coating, an enteric coating, a modified release coating, a protective coating, an anti-adhesive coating etc.

A solid dosage form according to the invention may also be coated in order to obtain suitable properties e.g. with respect to release of the active substance. The coating may be applied on single unit dosage forms (e.g. tablets, capsules) or it may be applied on a

polydepot dosage form or on its individual units.

Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.

In the following is given a more detailed description of interesting embodiments of the invention, i.e. embodiments wherein the solid dosage forms are designed to release tacrolimus and/or an analogue thereof in a modified or delayed manner. In the present context, the term "modified release" is intended to include all types of release which differ from the release obtained from plain tablets. Thus, the term includes so-called "controlled release", "sustained release", "pulsed release", "prolonged release", burst release", "slow release", "extended release", as well as the term "delayed release". However, a specific aspect of the invention relates to a delayed release composition or dosage form, which in this context is intended to denote a composition or dosage form that at the most releases 10% w/w of the active substance within the first 2 hours after administration and/or after start of a dissolution test employing a dissolution medium having a pH of at the most about 3.

Types of modified release systems

A first class includes matrix systems, in which tacrolimus is embedded or dispersed in a matrix of another material that serves to retard the release of tacrolimus into an aqueous environment (i.e., the luminal fluid of the GI tract). When tacrolimus is dispersed in a matrix of this sort, release of the drug takes place principally from the surface of the matrix. Thus the drug is released from the surface of a device, which incorporates the matrix after it diffuses through the matrix or when the surface of the device erodes, exposing the drug. In some embodiments, both mechanisms can operate simultaneously. The matrix systems may be large, i.e., tablet sized (about 1 cm), or small (< 0.3cm). The system may be unitary (e.g., a bolus), may be divided by virtue of being composed of several sub-units (for example, several capsules which constitute a single dose) which are administered substantially simultaneously, or may comprise a plurality of particles, also

denoted a multiparticulate. A multiparticulate can have numerous formulation applications. For example, a multiparticulate may be used as a powder for filling a capsule shell, or used *per se* for mixing with food to increase palatability.

In a specific embodiment, a matrix multiparticulate, comprises a plurality of tacrolimus-containing particles, each particle comprising tacrolimus and/or an analogue thereof e.g. in the form of a solid dispersion with one or more excipients selected to form a matrix capable of controlling the dissolution rate of the tacrolimus into an aqueous medium. The matrix materials useful for this embodiment are generally water-insoluble materials such as waxes, cellulose, or other water-insoluble polymers. If needed, the matrix materials may optionally be formulated with water-soluble materials, which can be used as binders or as enhancers. Matrix materials useful for the manufacture of these dosage forms such as: Hydroxypropyl methyl cellulose, waxes such as paraffin, modified vegetable oils, camauba wax, hydrogenated castor oil, beeswax, and the like, as well as synthetic polymers such as poly(vinyl chloride), poly(vinyl acetate), copolymers of vinyl acetate and ethylene, polystyrene, and the like. Water soluble binders or release modifying agents which can optionally be formulated into the matrix include water-soluble polymers such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, poly (N-vinyl-2-pyrrolidinone) (PVP), poly(ethylene oxide) (PEO), poly(vinyl alcohol) (PVA), xanthan gum, carrageenan, and other such natural and synthetic materials. In addition, materials, which function as release-modifying agents include water-soluble materials such as sugars or salts. Preferred water-soluble materials include lactose, sucrose, glucose, and mannitol, as well as HPC, HPMC, and PVP.

In a specific embodiment, a multiparticulate product is defined as being processed by controlled agglomeration. In this case tacrolimus is dispersed in a suitable meltable carrier and sprayed on carrier particles comprising the matrix substance. Alternatively, tacrolimus is dispersed in an organic solvent together with the matrix substance and spray dried or applied to carrier particles.

Solvents typically employed for the process include acetone, ethanol, isopropanol, ethyl acetate, and mixtures of two or more (for further details reference is given to the paragraphs under the heading Description of a solid dispersion based on organic solvents).

Once formed, tacrolimus matrix multiparticulates may be blended with compressible excipients such as lactose, microcrystalline cellulose, dicalcium phosphate, and the like

and the blend compressed to form a tablet. Disintegrants such as sodium starch glycolate or crosslinked poly(vinyl pyrrolidone) are also usefully employed. Tablets prepared by this method disintegrate when placed in an aqueous medium (such as the GI tract), thereby exposing the multiparticulate matrix, which releases tacrolimus therefrom.

A further embodiment of a matrix system has the form of a hydrophilic matrix tablet containing tacrolimus and/or an analogue thereof (e.g. in the form of a solid dispersion) as a multiparticulate product and an amount of hydrophilic polymer sufficient to provide a useful degree of control over the tacrolimus dissolution. Hydrophilic polymers useful for forming the matrix include hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), poly (ethylene oxide), poly(vinyl alcohol), xanthan gum, carbomer, carrageenan, and zooglan. A preferred material is HPMC. Other similar hydrophilic polymers may also be employed. In use, the hydrophilic material is swollen by, and eventually dissolves in, water. The tacrolimus is released both by diffusion from the matrix and by erosion of the matrix. The tacrolimus dissolution rate of these hydrophilic matrix tablets may be controlled by the amount and molecular weight of hydrophilic polymer employed. In general, using a greater amount of the hydrophilic polymer decreases the dissolution rate, as does using a higher molecular weight polymer. Using a lower molecular weight polymer increases the dissolution rate. The dissolution rate may also be controlled by the use of water-soluble additives such as sugars, salts, or soluble polymers. Examples of these additives are sugars such as lactose, sucrose, or mannitol, salts such as NaCl, KCl, $NaHCO_3$, and water soluble polymers such as PNVP or PVP, low molecular weight HPC or HMPC or methyl cellulose. In general, increasing the fraction of soluble material in the formulation increases the release rate. A matrix tablet typically comprises about 20 to 90% by weight of tacrolimus and about 80 to 10% by weight of polymer.

A preferred matrix tablet comprises, by weight, about 30% to about 80% solid dispersion containing tacrolimus and/or an analogue thereof about 15% to about 35% matrix former (such as, e.g., HPMC), 0% to about 35% lactose, 0% to about 20% microcrystalline cellulose, and about 0.25% to about 2% lubricant (such as, e.g., magnesium stearate).

The matrix systems as a class often exhibit non-constant release of the drug from the matrix. This result may be a consequence of the diffusive mechanism of drug release, and modifications to the geometry of the dosage form can be used to advantage to make the release rate of the drug more constant.

A second class of tacrolimus sustained-release dosage forms of this invention includes membrane-moderated or reservoir systems. In this class, a reservoir of tacrolimus e.g. in a solid dispersion as a multiparticulate product is surrounded by a rate-limiting membrane. The tacrolimus traverses the membrane by mass transport mechanisms well known in the art, including but not limited to dissolution in the membrane followed by diffusion across the membrane or diffusion through liquid-filled pores within the membrane. These individual reservoir system dosage forms may be large, as in the case of a tablet containing a single large reservoir, or multiparticulate, as in the case of a capsule or poly-depot tablets containing a plurality of reservoir particles, each individually coated with a membrane. The coating can be non-porous, yet permeable to tacrolimus (for example tacrolimus may diffuse directly through the membrane), or it may be porous. As with other embodiments of this invention, the particular mechanism of transport is not believed to be critical.

Sustained release coatings as known in the art may be employed to fabricate the membrane, especially polymer coatings, such as a cellulose ester or ether, an acrylic polymer, or a mixture of polymers. Preferred materials include ethyl cellulose, cellulose acetate and cellulose acetate butyrate. The polymer may be applied as a solution in an organic solvent or as an aqueous dispersion or latex. The coating operation may be conducted in standard equipment such as a fluid bed coater, a Wurster coater, or a rotary fluid bed coater.

If desired, the permeability of the coating may be adjusted by blending of two or more materials. A particularly useful process for tailoring the porosity of the coating comprises adding a pre-determined amount of a finely-divided water-soluble material, such as sugars or salts or water-soluble polymers to a solution or dispersion (e.g., an aqueous latex) of the membrane-forming polymer to be used. When the dosage form is ingested into the aqueous medium of the GI tract, these water soluble membrane additives are leached out of the membrane, leaving pores which facilitate release of the drug. The membrane coating can also be modified by the addition of plasticizers, as known in the art.

A particularly useful variation of the process for applying a membrane coating comprises dissolving the coating polymer in a mixture of solvents chosen such that as the coating dries, a phase inversion takes place in the applied coating solution, resulting in a membrane with a porous structure.

In general, a support for mechanically strengthening the membrane is not required.

The morphology of the membrane is not of critical importance so long as the permeability characteristics enumerated herein are met. The membrane can be amorphous or crystalline. It can have any category of morphology produced by any particular process and can be, for example, an interfacially-polymerized membrane (which comprises a thin rate-limiting skin on a porous support), a porous hydrophilic membrane, a porous hydrophobic membrane, a hydrogel membrane, an ionic membrane, and other such materials which are characterized by controlled permeability to tacrolimus.

A sustained release coating as known in the art, especially polymer coatings, may be employed to fabricate the membrane. Suitable and preferred polymer coating materials, equipment, and coating methods also include those previously discussed.

The rate of tacrolimus release from the coated multiparticulates can also be controlled by factors such as the composition and binder content of the drug-containing core, the thickness and permeability of the coating, and the surface-to-volume ratio of the multiparticulates. It will be appreciated by those skilled in the art that increasing the thickness of the coating will decrease the release rate, whereas increasing the permeability of the coating or the surface-to-volume ratio of the multiparticulates will increase the release rate. If desired, the permeability of the coating may be adjusted by blending of two or more materials. A useful series of coatings comprises mixtures of water-insoluble and water-soluble polymers, for example, ethylcellulose and hydroxypropyl methylcellulose, respectively. A particularly useful modification to the coating is the addition of finely-divided water-soluble material, such as sugars or salts. When placed in an aqueous medium, these water soluble membrane additives are leached out of the membrane, leaving pores which facilitate delivery of the drug. The membrane coating may also be modified by the addition of plasticizers, as is known to those skilled in the art.

In one embodiment of the invention it is an aim to reduce the exposure of the upper GI tract to high concentrations of tacrolimus. Accordingly, suitable dosage forms includes those forms, which incorporate a delay before the onset of sustained release of tacrolimus. An exemplary embodiment can be illustrated by a tablet (or a particulate material) comprising a core containing tacrolimus coated with a first coating of a polymeric material of the type useful for sustained release of tacrolimus and a second coating of the

type useful for delaying release of drugs when the dosage form is ingested. The first coating is applied over and surrounds the tablet or individual particles. The second coating is applied over and surrounds the first coating.

A tablet can be prepared by techniques well known in the art and contains a therapeutically useful amount of tacrolimus plus such excipients as are necessary to form the tablet by such techniques.

The first coating may be a sustained release coating as known in the art, especially polymer coatings, to fabricate the membrane, as previously discussed for reservoir systems. Suitable and preferred polymer coating materials, equipment, and coating methods also include those previously discussed.

Materials useful for preparing the second coating on the tablet include polymers known in the art as enteric coatings for delayed-release of pharmaceuticals. These most commonly are pH-sensitive materials such as cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose phthalate, poly (vinyl acetate phthalate), and acrylic copolymers such as Eudragit L-100 (Röhm Pharma) and related materials, as more fully detailed below under "Delayed Release". The thickness of the delayed-release coating is adjusted to give the desired delay property. In general, thicker coatings are more resistant to erosion and, consequently, yield a longer delay. Preferred coatings range from about 300 μm in thickness to about 3 mm in thickness.

When ingested, the twice-coated tablet passes through the stomach, where the second coating prevents release of the tacrolimus under the acidic conditions prevalent there. When the tablet passes out of the stomach and into the small intestine, where the pH is higher, the second coating erodes or dissolves according to the physicochemical properties of the chosen material. Upon erosion or dissolution of the second coating, the first coating prevents immediate or rapid release of the tacrolimus and modulates the release so as to prevent the production of high concentrations, thereby minimizing side-effects.

A further preferred embodiment comprises a multiparticulate wherein each particle is dual coated as described above for tablets, first with a polymer designed to yield sustained release of the tacrolimus and then coated with a polymer designed to delay onset of release in the environment of the GI tract when the dosage form is ingested.

The sustained release coating may be as known in the art, especially polymer coatings, to fabricate the membrane, as previously discussed for reservoir systems. Suitable and preferred polymer coating materials, equipment, and coating methods also include those previously discussed.

The rate of tacrolimus release from the sustained-release-coated multiparticulates (i.e., the multiparticulates before they receive the delayed-release coating) and methods of modifying the coating are also controlled by the factors previously discussed for reservoir system tacrolimus multiparticulates.

The second membrane or coating for dual coated multiparticulates is a delayed-release coating which is applied over the first sustained-release coating, as disclosed above for tablets, and may be formed from the same materials. It should be noted that the use of the so-called "enteric" materials to practice this embodiment differs significantly from their use to produce conventional enteric dosage forms. With conventional enteric forms, the object is to delay release of the drug until the dosage form has passed the stomach and then to deliver the dose in the duodenum. Dosing of tacrolimus directly and completely to the duodenum may be undesirable, however, due to the side effects sought to be minimized or avoided by this invention. Therefore, if conventional enteric polymers are to be used to practice this embodiment, it may be necessary to apply them significantly more thickly than in conventional practice, in order to delay drug release until the dosage form reaches the lower GI tract. However, it is also possible to effect a sustained or controlled delivery of tacrolimus after the delayed-release coating has dissolved or eroded, therefore the benefits of this embodiment may be realized with a proper combination of delayed-release character with sustained-release character, and the delayed-release part alone may or may not necessarily conform to USP enteric criteria. The thickness of the delayed-release coating is adjusted to give the desired delay property. In general, thicker coatings are more resistant to erosion and, consequently, yield a longer delay.

A first delayed release embodiment according to the invention is a "pH-dependent coated tablet", which comprises a tablet core comprising tacrolimus e.g. in a solid dispersion as a multiparticulate product, a disintegrant, a lubricant, and one or more pharmaceutical carriers, such core being coated with a material, preferably a polymer, which is substantially insoluble and impermeable at the pH of the stomach, and which is more soluble and permeable at the pH of the small intestine. Preferably, the coating polymer is substantially insoluble and impermeable at pH <5.0, and water-soluble at pH>5.0. The tablet core may be coated with an amount of polymer sufficient to assure that substantially

no release of tacrolimus from the dosage form occurs until the dosage form has exited the stomach and has resided in the small intestine for about 15 minutes or greater, preferably about 30 minutes or greater, thus assuring that minimal tacrolimus is released in the duodenum. Mixtures of a pH-sensitive polymer with a water-insoluble polymer may also be employed. Tablets are coated with an amount of polymer comprising from about 10% to about 80% of the weight of the tacrolimus-containing tablet core. Preferred tablets are coated with an amount of polymer comprising about 15% to about 50% of the weight of the tacrolimus tablet core.

pH-sensitive polymers which are relatively insoluble and impermeable at the pH of the stomach, but which are more soluble and permeable at the pH of the small intestine and colon include polyacrylamides, phthalate derivatives such as acid phthalates of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate, styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers, polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, shellac, and vinyl acetate and crotonic acid copolymers.

Preferred pH-sensitive polymers include shellac; phthalate derivatives, particularly cellulose acetate phthalate, polyvinylacetate phthalate, and hydroxypropylmethylcellulose phthalate; polyacrylic acid derivatives, particularly polymethyl methacrylate blended with acrylic acid and acrylic ester copolymers; and vinyl acetate and crotonic acid copolymers.

Cellulose acetate phthalate (CAP) may be applied to tacrolimus tablets to provide delayed release of tacrolimus until the tacrolimus-containing tablet has passed the sensitive duodenal region, that is to delay the release of tacrolimus in the gastrointestinal tract until about 15 minutes, and preferably about 30 minutes, after the tacrolimus-containing tablet has passed from the stomach to the duodenum. The CAP coating solution may also contain one or more plasticizers, such as diethyl phthalate, polyethyleneglycol-400, triacetin, triacetin citrate, propylene glycol, and others as known in the art. Preferred plasticizers are diethyl phthalate and triacetin. The CAP coating formulation may also contain one or more emulsifiers, such as polysorbate-80.

Anionic acrylic copolymers of methacrylic acid and methylmethacrylate are also particularly useful coating materials for delaying the release of tacrolimus from tacrolimus-containing tablets until the tablets have moved to a position in the small intestine, which is distal to the duodenum. Copolymers of this type are available from RöhmPharma Corp, under the tradenames Eudragit-L® and Eudragit-S®. Eudragit-L® and Eudragit-S® are anionic copolymers of methacrylic acid and methylmethacrylate. The ratio of free carboxyl groups to the esters is approximately 1:1 in Eudragit-L® and approximately 1:2 in Eudragit-S®. Mixtures of Eudragit-L® and Eudragit-S® may also be used. For coating of tacrolimus-containing tablets, these acrylic coating polymers must be dissolved in an organic solvent or mixture of organic solvents. Useful solvents for this purpose are acetone, isopropyl alcohol, and methylene chloride. It is generally advisable to include 5-20% placticizer in coating formulations of acrylic copolymers. Useful plasticizers are polyethylene glycols, propylene glycols, diethyl phthalate, dibutyl phthalate, castor oil, and triacetin.

The delay time before release of tacrolimus, after the "pH-dependent coated tablet" dosage form has exited the stomach, may be controlled by choice of the relative amounts of Eudragit-L® and Eudragit-S® in the coating, and by choice of the coating thickness. Eudragit-L® films dissolve above pH 6.0, and Eudragit-S® films dissolve above 7.0, and mixtures dissolve at intermediate pH's. Since the pH of the duodenum is approximately 6.0 and the pH of the colon is approximately 7.0, coatings composed of mixtures of Eudragit-L® and Eudragit-S® provide protection of the duodenum from tacrolimus. If it is desired to delay release of tacrolimus until the tacrolimus-containing "pH-dependent coated tablet" has reached the colon, Eudragit-S® may be used as the coating material, as described by Dew et al (Br. J. Clin. Pharmac. 14 (1982) 405-408). In order to delay the release of tacrolimus for about 15 minutes or more, preferably 30 minutes or more, after the dosage form has exited the stomach, preferred coatings comprise from about 9:1 to about 1:9 Eudragit-L® /Eudragit-S®, more preferably from about 9:1 to about 1:4 Eudragit-L® /Eudragit-S® . The coating may comprise from about 3% to about 70% of the weight of the uncoated tablet core. Preferably, the coating comprises from about 5% to about 50% of the weight of the tablet core.

The invention is further illustrated in the following examples without limiting it thereto.

Methods

Determination of weight variation

The tablets prepared in the Examples herein were subject to a test for weight variation performed in accordance with Ph. Eur.

Determination of average tablet hardness

The tablets prepared in the Examples herein were subject to at test for tablet hardness employing Schleuniger Model 6D apparatus and performed in accordance with the general instructions for the apparatus.

Determination of disintegration time

The time for a tablet to disintegrate, i.e. to decompose into particles or agglomerates, was determined in accordance with Ph. Eur.

Determination of geometric weight mean diameter d_{gw}

The geometric weight mean diameter was determined by employment of a method of laser diffraction dispersing the particulate material obtained (or the starting material) in air. The measurements were performed at 1 bar dispersive pressure in Sympatec Helos equipment, which records the distribution of the equivalent spherical diameter. This distribution is fitted to a log normal volume-size distribution.

When used herein, "geometric weight mean diameter" means the mean diameter of the log normal volume-size distribution.

Determination of dissolution rate

The dissolution rate was determined by employment of USP paddle dissolution method at 37 °C.

Examples

For the preparation of a pharmaceutical composition in particulate form according to the invention the method described in WO 03/004001 (by the present inventors) has been employed. The method ensures a controlled agglomeration process, i.e. a strict control of the growth in particle size while at the same time it is possible to use a relatively large amount of an oil or an oily-like material.

Examples on Tacrolimus formulation based on controlled agglomeration

HPMC refers to Metolose 90 SH (type 2208) or Metolose 60 SH (type 2910) from ShinEtsu, available in different degree of polymerisation (viscosity, 3-100.000 cP) Either tablets, capsules or granules might be enteric coated with different types of polymers such as hydroxypropylmethylcellulose acetate succinate (Aqoat), cellulose acetate phthalate CAP, hydroxypropylmethylcellulose phtalate HPMCP or methacrylic acid copolymers such as Eudragit L30D, Eudragit 100/S, Eudragit 100/L

Example 1
Immediate release tablet with improved bioavailability

Substances	%	mg
Tacrolimus	0.50	1.00
Lactose 200 mesh	49.75	100.00
PEG 6000	34.48	69.30
Poloxamer 188	14.78	29.70
Magnesium stearate	0.50	1.01
Total	100.00	201.01

Tacrolimus is dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

The mixture is compressed into 8 mm tablets with a strength of 1 mg (200 mg tablet with compound cup shaped.
Mean disintegration time: 20 min, Hardness: 45 N

Example 2
Modified release polydepot capsule based on swelling hydrocolloid matrix of hydroxypropylcellulose

Substance	%	mg
Tacrolimus	0.50	1.00
HPMC	20.00	40.00
Lactose 200 mesh	30.00	60.00
PEG 6000	34.65	69.30
Poloxamer 188	14.85	29.70
Total	100.00	200.00

Tacrolimus is dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The solution is sprayed on a mixture of 150 lactose and 100 g HPMC in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg)

Example 3

Modified release polydepot capsule based on swelling hydrocolloid matrix of hydroxypropylcellulose

Substance	%	mg
Tacrolimus	0.50	1.00
HPMC 2910 3 cp	20.00	40.00
Lactose 200 mesh	30.00	60.00
Glyceryl monostearate	49.50	99.00
Total	100.00	200,00

Tacrolimus is dissolved in Glycerylmonostearate at 70 °C. The solution is sprayed on a mixture of 150 lactose and 100 g HPMC in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg)

Example 4

Modified release matrix tablet based on swelling hydrocolloid matrix of hydroxypropylcellulose

Substance	%	mg
Tacrolimus	0.50	1.00
HPMC	19.90	40.00
Lactose 200 mesh	29.85	60.00

PEG 6000	34.48	69.30
Poloxamer 188	14.78	29.70
Magnesium stearate	0.50	1.01
Total	100.00	201.01

Tacrolimus is dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and blended with HPMC and magnesium stearate for 0.5 min in a Turbula mixer.

The mixture is compressed into 8 mm tablets with a strength of 1 mg (200 mg tablet with compound cup shaped.
Mean disintegration time: 20 min, Hardness: 45 N

Example 5
Modified release matrix tablet based on lipophilic matrix of glyceryl monostearate

Substance	%	mg
Tacrolimus	0.50	1.00
Lactose 200 mesh	49.75	100.00
Glycerylmonostearate	49.25	99.00
Magnesium stearate	0.50	1.01
	100.00	201.01

Tacrolimus is dissolved in Glyceryl monostearate at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.
The mixture is compressed into 8 mm tablets with a strength of 1 mg (200 mg tablet with compound cup shape.
Mean disintegration time: 20 min, Hardness: 45 N

Example 6
Modified release polydepot capsule based on lipophilic matrix of glyceryl-monostearate

Substance	%	mg
Tacrolimus	0.50	1.00
Lactose 200 mesh	49.75	100.00
Glycerylmonostearate	49.25	99.00
Magnesium stearate	0.50	1.01
	100.00	201.01

Tacrolimus is dissolved in Glyceryl monostearate at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg).

Example 7

Modified release polydepot Tablet based on lipophilic matrix of gelucire 44/14

Substance	%	mg
Tacrolimus	0.50	1.00
Aeroperl 300	49.75	100.00
Gelucire 44/14	49.25	99.00
Magnesium stearate	0.50	1.01
	100.00	201.01

Tacrolimus is dissolved in gelucire at 70 °C. The solution is sprayed on 250 g aeroperl in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg).

The granulate is compressed into 8 mm tablets with strength of 1 mg (tablet weight 200 mg). Tablets are cup shaped.

Mean disintegration time: 25 min, Hardness: 43 N

Claims

1. A pharmaceutical composition in particulate form comprising tacrolimus or analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and exhibits an $AUC/AUC_{Prograf}$ value of at least about 1.3, the AUC values being determined under similar conditions.

2. A pharmaceutical composition according to claim 1, wherein the $AUC/AUC_{Prograf}$ value is at least about 1.5 such as about 1.75 or more, about 1.8 or more, about 1.9 or more, about 2.0 or more, about 2.5 or more, about 2.75 or more, about 3.0 or more, about 3.25 or more, about 3.5 or more, about 3.75 or more, about 4.0 or more, about 4.25 or more, about 4.5 or more, about 4.75 or more or about 5.0 or more, the AUC values being determined under similar conditions.

3. A pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and does not exhibit a significant adverse food effect as evidenced by a value of (AUC_{fed}/AUC_{fasted}) of at least about 0.85 with a lower 90% confidence limit of at least 0.75.

4. A pharmaceutical composition according to claim 3, wherein the value of (AUC_{fed}/AUC_{fasted}) is about 0.9 or more such as, e.g., about 0.95 or more, about 0.97 or more or about 1 or more.

5. A pharmaceutical composition in particulate form comprising tacrolimus together or an analogue thereof with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and the composition being essentially bioequivalent with Prograf® or a similar commercially available tacrolimus-containing product when administered in a dosis that is at the about most about 85% w/w of the dose of tacrolimus administered in the form of Prograf® or a similar commercially available tacrolimus-containing product.

6. A pharmaceutical composition according to claim 5, wherein the dose is at the most about 80% w/w such as, e.g., at the most about 75%, at the most about 70% w/w, at the

most about 65% w/w, at the most about 60% w/w, at the most about 55% w/w or at the most about 50% w/w of the dose of tacrolimus administered in the form of Prograf® or a similar commercially available tacrolimus-containing product.

7. A pharmaceutical composition according to claim 5 or 6, wherein the bioequivalence is determined by means of at least one of the following parameters: t_{max}, c_{max}, AUC_{0-t}, $AUC_{0-infinity}$, W_{50}, W_{75} and/or MRT.

8. A pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and reduces gastro-intestinal side effects compared to those of Prograf® administered under the same conditions and in a dose that provides an equivalent therapeutic effect.

9. A pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and reduces inter- and/or intra-individual variations compared to those of Prograf® administered under the same conditions and in a dose that provides an equivalent therapeutic effect.

10. A pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof in a pH-dependant manner releases at least about 50% w/w of the total amount of tacrolimus or an analogue thereof within about 15 hours such as, e.g., within about 12 hours.

11. A pharmaceutical composition according to claim 10, wherein the composition upon oral administration to a mammal in need thereof releases at least about 50% w/w of the total amount of tacrolimus or an analogue thereof within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours or within about 3 hours.

12. A pharmaceutical composition according to claim 10 or 11, wherein the composition upon oral administration to a mammal in need thereof releases at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an

analogue thereof within about 15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours.

13. A pharmaceutical composition according to claim 10, wherein at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

14. A pharmaceutical composition according to any of claims 10-13, wherein at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours, within about 3 hours or within about 2 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

15. A pharmaceutical composition according to claim 14, wherein at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 1.5 hours such as, e.g., within about 1 hour, within about 0.75 hours, within about 0.5 hours or within about 20 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

16. A pharmaceutical composition according to any of claims 10-15, wherein at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof is released within about 15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

17. A pharmaceutical composition according to any of claims 10-15, wherein at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof is released within about 5 hours such as, e.g., within about 4 hours, within about 3 hours, within about 2 hours, within about 1 hours or within about 30 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

18. A pharmaceutical composition according to any of claims 13-17, wherein the in vitro dissolution test is carried out employing USP dissolution test (paddle) and a buffer pH 7.5 containing 2.5% SDS and 1g/mL of pancreatin as dissolution medium.

19. A pharmaceutical composition according to claim 10, wherein at least about 20% w/w such as, e.g., at least about 25% w/w, at least about 30% w/w, at least about 35% w/w or at least about 40% w/w of the total amount of tacrolimus or an analogue thereof is released within the first 3 hours such as, e.g., within the first 2 hours or within the first hour when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

20. A pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof has a delayed release of tacrolimus or an analogue thereof so that at the most about 10% w/w such as, e.g., at the most about 7.5% w/w or at the most about 5% w/w of the total amount of tacrolimus or an analogue thereof is released within the first two hours such as, e.g., within the first hour after administration.

21. A pharmaceutical composition according to claim 20, wherein at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w, at the most about 15% w/w or at the most about 10% w/w of tacrolimus or an analogue thereof is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

22. A pharmaceutical composition according to claim 20 or 21, wherein at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 5% w/w or at the most about 2.5% w/w of tacrolimus or an analogue thereof is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

23. A pharmaceutical composition according to any of claims 20-22, wherein at the most about 60% w/w such as, e.g., at the most about 50% w/w, at the most about 40% w/w or at the most about 30% w/w of tacrolimus or an analogue thereof is released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro dissolution test

employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

24. A pharmaceutical composition according to any of claims 20-23, wherein at the most about 40% w/w such as, e.g., at the most about 30% w/w, at the most about 25% w/w or at the most about 20% w/w of tacrolimus or an analogue thereof is released within 6 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

25. A pharmaceutical composition according to any of claims 20-24, wherein at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w or at the most about 15% w/w of tacrolimus or an analogue thereof is released within 4 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

26. A pharmaceutical composition according to any of the preceding claims, wherein the particulate material has a geometric weight mean diameter d_{gw} of ≥ 10 μm such as, e.g. $\geq$ 20 μm, from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500 μm, from about 100 to about 1000 μm or from about 100 to about 700 μm, or at the most about 400 μm or at the most 300 μm such as, e.g., from about 50 to about 400 μm such as, e.g., from about 50 to about 350 μm, from about 50 to about 300 μm, from about 50 to about 250 μm or from about 100 to about 300 μm.

27. A pharmaceutical composition according to any of the preceding claims, wherein the one or more pharmaceutically acceptable excipient is selected from the group consisting of fillers, disintegrants, binders, diluents, lubricants and glidants.

28. A pharmaceutical composition according to any of the preceding claims further comprising an pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents.

29. A pharmaceutical composition according to any of the preceding claims wherein at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

30. A pharmaceutical composition according to any of the preceding claims comprising a silica acid or a derivative or salt thereof.

31. A pharmaceutical composition any of the preceding claims comprising silicon dioxide or a polymer thereof.

32. A pharmaceutical composition according to any of the preceding claims comprising a silicon dioxide product that has properties corresponding to Zeofree® 5161A, Zeofree® 5162, Zeofree® 5175A, Zeopharm® 80 (available from J. M. Huber, Hamina, Finland), Aeroperl® 300, Sident® 22S, Sipernat®160, Sipernat® 160PQ, Sipernat® 22, Sipernat® 22 LS, Sipernat® 22, Sipernat® 22 LS, Sipernat® 22S, Sipernat® 2200, Sipernat® 310, Sipernat® 320, Sipernat® 320 DS, Sipernat® 325 C, Sipernat® 35, Sipernat® 350, Sipernat® 360, Sipernat® 383 D8, Sipernat® 44, Sipernat® 44MS, Sipernat® 50, Sipernat® 50S, Sipernat® 50 S, Sipernat® 500 LS, or Sipernat® 570 (available from Degussa, Frankfurt, Germany).

33. A pharmaceutical composition according to any of the preceding claims comprising an oil or an oily-like material

34. A pharmaceutical composition according to claim 33, wherein the concentration of the oil or oily-like material in the composition is about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more.

35. A pharmaceutical composition according to claim 34, wherein the concentration of the oil or oily-like material is in a range from about 20% to about 80% w/w such as, e.g., from about 25% to about 75% w/w.

36. A pharmaceutical composition according to any of the preceding claims, wherein at least a part of tacrolimus or an analogue thereof, is present in the form of a solid dispersion including a molecular dispersion and a solid solution.

37. A pharmaceutical composition according to claim 36, wherein the solid dispersion is manufactured by dissolving at least a part of tacrolimus or an analogue thereof in an organic solvent containing a material suitable for forming solid dispersions and subsequent removing the organic solvent e.g. by evaporation.

38. A pharmaceutical composition according to claim 37, wherein the material suitable for forming solid dispersions is selected from the group consisting of cellulose derivatives including hydroxypropylmethylcellulose, NaCMC, PVP and PVA.

39. A pharmaceutical composition according to any of the preceding claims having an acceptable flowability as determined according to the method described in Ph.Eur. measuring the flow rate of the material out of a funnel with a nozzle diameter of 10.0 mm.

40. A pharmaceutical composition according to any of the preceding claims for use in the manufacture of granules, pellets, microspheres, nanoparticles.

41. A pharmaceutical composition according to any of the preceding claims for use in the manufacture of a solid dosage form.

42. A pharmaceutical composition according to claim 41, wherein the solid dosage form is intended for administration via the oral, buccal or sublingual administration route.

43. A pharmaceutical composition according to claim 41 or 42 in the form of tablets, capsules or sachets.

44. A pharmaceutical composition according to any of the preceding claims for use in the manufacture of tablets obtained by direct compression.

45. A solid dosage form comprising a pharmaceutical composition according to any of claims 1-44.

46. A solid dosage form according to claim 45, wherein the concentration of the pharmaceutical composition in particulate form is in a range of from about 5% to 100% w/w such as, e.g., from about 10% to about 90% w/w, from about 15% to about 85% w/w, from about 20% to about 80% w/w, from about 25% to about 80% w/w, from about 30% to about 80% w/w, from about 35% to about 80% w/w, from about 40% to about 75% w/w, from about 45% to about 75% w/w or from about 50% to about 70% w/w of the dosage form.

47. A solid dosage form according to claim 45, wherein the concentration of the pharmaceutical composition in particulate form is 50% w/w or more of the dosage form.

48. A solid dosage form according to any of claims 45-47, wherein the solid dosage form upon oral administration to a mammal in need thereof exhibits an $AUC/AUC_{Prograf®}$ value of at least about 1.3, the AUC values being determined under similar conditions.

49. A solid dosage form according to claim 48, wherein the $AUC/AUC_{Prograf®}$ value is at least about 1.5 such as about 1.75 or more, about 1.8 or more, about 1.9 or more, about 2.0 or more, about 2.5 or more, about 2.75 or more, about 3.0 or more, about 3.25 or more, about 3.5 or more, about 3.75 or more, about 4.0 or more, about 4.25 or more, about 4.5 or more, about 4.75 or more or about 5.0 or more, the AUC values being determined under similar conditions.

50. A solid dosage form according to any of claims 45-50, wherein the solid dosage form releases tacrolimus or an analogue thereof in a pH-dependant manner and does not exhibit a significant adverse food effect as evidenced by a value of (AUC_{fed}/AUC_{fasted}) of at least about 0.85 with a lower 90% confidence limit of at least 0.75.

51. A solid dosage form according to claim 50, wherein the value of (AUC_{fed}/AUC_{fasted}) is about 0.9 or more such as, e.g., about 0.95 or more, about 0.97 or more or about 1 or more.

52. A solid dosage form according to any of claims 45-51, wherein the solid dosage form upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and the solid dosage form being essentially

bioequivalent with Prograf® or a similar commercially available tacrolimus-containing product when administered in a dose that is at the most about 85% w/w of the dose of Tacrolimus administered in the form of Prograf® or a similar commercially available Tacrolimus containing product.

53. A solid dosage form according to claim 52, wherein the dose is at the most about 80% w/w such as, e.g., at the most about 75%, at the most about 70% w/w, at the most about 65% w/w, at the most about 60% w/w, at the most about 55% w/w or at the most about 50% w/w of the dose of tacrolimus administered in the form of Prograf® or a similar commercially available tacrolimus-containing product.

54. A solid dosage form according to claim 52 or 53, wherein the bioequivalence is determined by means of at least one of the following parameters: t_{max}, c_{max}, AUC_{0-t}, $AUC_{0-infinity}$, W_{50}, W_{75} and/or MRT.

55. A solid dosage form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the solid dosage form upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and reduces gastro-intestinal side effects compared to those of Prograf® administered under the same conditions and in a dose that provides an equivalent therapeutic effect.

56. A solid dosage form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the solid dosage form upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a pH-dependant manner and reduces inter- and/or intra-individual variations compared to those of Prograf® administered under the same conditions and in a dose that provides an equivalent therapeutic effect.

57. A solid dosage form according to any of claims 45-56, wherein the solid dosage form upon oral administration to a mammal in need thereof releases at least about 50% w/w of the total amount of tacrolimus or an analogue thereof within about 15 hours such as, e.g., within about 12 hours.

58. A solid dosage form according to claim 57, wherein the solid dosage form upon oral administration to a mammal in need thereof releases at least about 50% w/w of the total

amount of tacrolimus or an analogue thereof within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours or within about 3 hours.

59. A solid dosage form according to claim 57 or 58, wherein the solid dosage form upon oral administration to a mammal in need thereof releases at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof within about 15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours.

60. A solid dosage form according to claim 57, wherein at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

61. A solid dosage form according to any of claims 57-60, wherein at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours, within about 3 hours or within about 2 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

62. A solid dosage form according to claim 61, wherein at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 1.5 hours such as, e.g., within about 1 hour, within about 0.75 hours, within about 0.5 hours or within about 20 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

63. A solid dosage form according to any of claims 58-62, wherein at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof is released within about 15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

64. A solid dosage form according to any of claims 58-63, wherein at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an

analogue thereof is released within about 5 hours such as, e.g., within about 4 hours, within about 3 hours, within about 2 hours, within about 1 hours or within about 30 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

65. A solid dosage form according to any of claims 60-64, wherein the in vitro dissolution test is carried out employing USP dissolution test (paddle) and a buffer pH 7.5 containing 2.5% SDS and 1g/mL of pancreatin as dissolution medium.

66. A solid dosage form according to claim 57, wherein at least about 20% w/w such as, e.g., at least about 25% w/w, at least about 30% w/w, at least about 35% w/w or at least about 40% w/w of the total amount of tacrolimus or an analogue thereof is released within the first 3 hours such as, e.g., within the first 2 hours or within the first hour when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

67. A solid dosage form according to any of claims 45-47, wherein the solid dosage form upon oral administration to a mammal in need thereof has a delayed release of tacrolimus or an analogue thereof so that at the most about 10% w/w such as, e.g., at the most about 7.5% w/w or at the most about 5% w/w of the total amount of tacrolimus or an analogue thereof is released within the first two hours such as, e.g., within the first hour after administration.

68. A solid dosage form according to claim 67, wherein at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w, at the most about 15% w/w or at the most about 10% w/w of tacrolimus or an analogue thereof is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

69. A solid dosage form according to claim 67 or 68, wherein at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 5% w/w or at the most about 2.5% w/w of tacrolimus or an analogue thereof is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

70. A solid dosage form according to any of claims 67-69, wherein at the most about 60% w/w such as, e.g., at the most about 50% w/w, at the most about 40% w/w or at the most about 30% w/w of tacrolimus or an analogue thereof is released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

71. A solid dosage form according to any of claims 67-70, wherein at the most about 40% w/w such as, e.g., at the most about 30% w/w, at the most about 25% w/w or at the most about 20% w/w of tacrolimus or an analogue thereof is released within 6 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

72. A solid dosage form according to any of claims 67-71, wherein at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w or at the most about 15% w/w of tacrolimus or an analogue thereof is released within 4 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

73. A solid dosage form according to any of claims 45-72 comprising a multiplicity of individual units such as, e.g., pellets, beads and/or granules.

74. A solid dosage form according to any of claims 45-73 in the form of tablets, capsules or sachets.

75. A solid dosage form according to claim 74 in the form of a tablet.

76. A solid dosage form according to any of claims 73-75, wherein the individual units or solid dosage form are coated with a coating selected from the group consisting of film coatings, modified release coatings, enteric coatings, protective coatings and anti-adhesive coatings.

77. A solid dosage form according to any of claims 45-76, wherein the amount of tacrolimus or an analogue thereof contained therein corresponds to a daily dose thereof.

78. A solid dosage form according to any of claims 45-77, wherein tacrolimus is embedded in a matrix that releases tacrolimus by diffusion.

79. A solid dosage form according to claim 78, wherein the matrix remains substantially intact during the period of drug release.

80. A solid dosage form according to any of claims 45-78, wherein tacrolimus is embedded in a matrix that release tacrolimus by eroding.

81. A solid dosage form according to any of claims 45-77, wherein tacrolimus is released from the dosage form by diffusion through a substantially water-insoluble coating.

82. A solid dosage form according to any of claims 45-77 in the form of a polydepot dosage form, which - upon administration - disintegrates into a multiplicity of individual units from which tacrolimus is released.

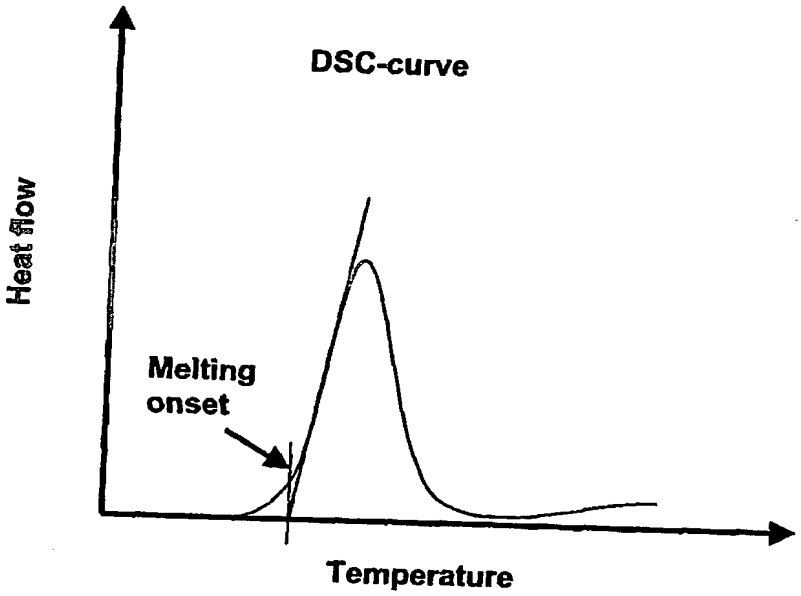


Fig. 1